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PCT

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International Bureau

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(54) Title: BIS MONO-AND BICYCLIC ARYL AND HETEROARYL COMPOUNDS WHICH INHIBIT EGF AND/OR PDGF RECEPTOR TYROSINE KINASE

(57) Abstract

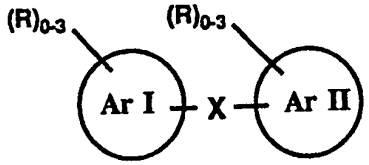
This invention relates to bis mono- and/or bicyclic aryl and/or heteroaryl compounds exhibiting protein tyrosine kinase inhibition activity. More specifically, it relates to the method of inhibiting abnormal cell proliferation in a patient suffering from a disorder characterized by such proliferation comprising the administration thereto of an EGF and/or PDGF receptor inhibiting effective amount of said bis mono- and/or bicyclic aryl and/or heteroaryl compound and to the preparation of said compounds and their use in pharmaceutical compositions used in this method.

WE CLAIM:

1. A method of inhibiting abnormal cell proliferation in a patient suffering from a disorder characterized by such proliferation comprising the administration thereto of an EGF and/or PDGF receptor inhibiting effective amount of a compound having a bis ring system wherein the first ring is aryl or heteroaryl and the second ring is aryl, heteroaryl, carbocyclic or heterocarbocyclic and wherein said rings comprise either a substituted or unsubstituted monocyclic ring containing 0 to about 2 hetero atoms, or a bicyclic ring containing 0 to about 4 hetero atoms, or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition for inhibiting abnormal cell proliferation comprising, in admixture with a pharmaceutically acceptable carrier, a pharmaceutically effective amount of a compound according to claim 1.

3. A method according to claim 1 comprising administering to said patient a pharmaceutically effective amount of a pharmaceutical composition containing, in admixture with a pharmaceutically acceptable carrier, a compound, or a pharmaceutically acceptable salt thereof, of the formula:



wherein

Ar I is a substituted or unsubstituted mono- or bicyclic aryl or heteroaryl ring system of about 5 to about 12 atoms and where each monocyclic ring may contain 0 to about 3 hetero atoms, and each bicyclic ring may contain 0 to about 4 hetero atoms selected from N, O and S provided said hetero atoms are not vicinal oxygen and/or sulfur atoms and where the substituents may be located at any appropriate position of the ring system and are described by R.;

Ar II may be as described for Ar I or it may also be saturated carbocyclic wherein said ring comprises either a substituted or unsubstituted

monocyclic ring containing 0 to about 2 hetero atoms, or a bicyclic ring containing 0 to about 4 hetero atoms;

X is $(CHR_1)_{0-4}$ or $(CHR_1)_m$-Z-$(CHR_1)_n$;

Z is O, NR', S, SO or SO_2;

m and n are 0-3 and m+n=0-3;

R substitution besides hydrogen independently includes alkyl, alkenyl, phenyl, aralkyl, aralkenyl, hydroxy, alkoxy, aralkoxy, acyloxy, halo, haloalkyl, amino, mono-and di-alkylamino, acylamino, carboxy, carbalkoxy, carbaralkoxy, carbalkoxyalkyl, carbalkoxyalkenyl, amido, mono- and dialkylamido and N,N-cycloalkylamido;

R and R together may also be keto;

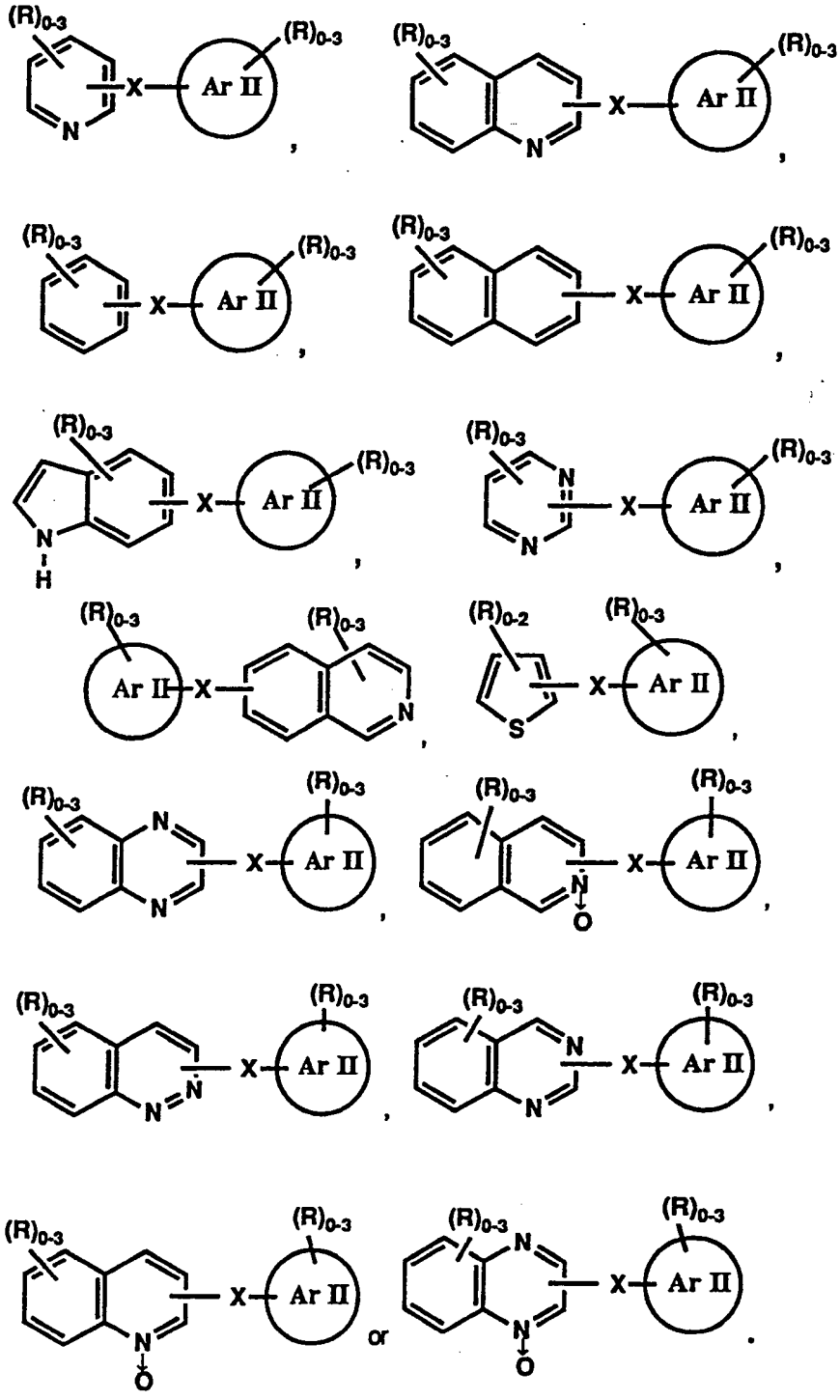
R_1 and R' are hydrogen or alkyl; or

a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition for inhibiting cell proliferation comprising, in admixture with a pharmaceutically acceptable carrier, a pharmaceutically effective amount of a compound according to claim 3.

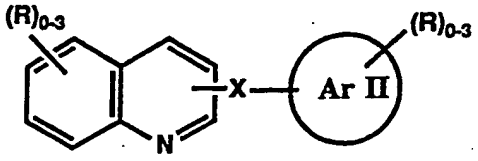
5. A method according to claim 3 where **Ar I** and **Ar II** are independently selected from phenyl, naphthyl, 2-(1H)pyridonyl, pyridyl, quinolinyl, thienyl, 1(2H)-isoquinolonyl, indolyl, napthyridenyl, benzothiazolyl, quinoxalinyl, benzomidazolyl, quinolinyl-N-oxide, isoquinolinyl-N-oxide, quinazolinyl, quinoxalinyl-N-oxide, quinazolinyl-N-oxide, benzoxazinyl, phthalazinyl, or cinnolinyl; and R is selected from hydrogen, alkyl, alkoxy, hydroxy, halo or trifluoromethyl.

6. A method according to claim 5 where said compound is described by one of the following formulae:



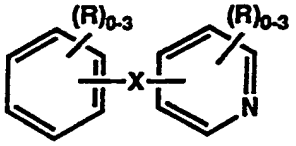
5

7. A method according to claim 6 where said compound is of the formula

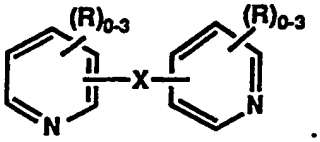


where Ar II is thienyl, phenyl, pyridyl, quinolinyl, indolyl, furanyl, imidazolyl, 2(1H)-pyridonyl, 1(2H)-isoquinolonyl and thiazolyl and R is hydrogen, loweralkyl, loweralkoxy, hydroxy or halo.

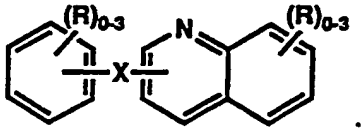
8. A method according to claim 6 where said compound is of the formula



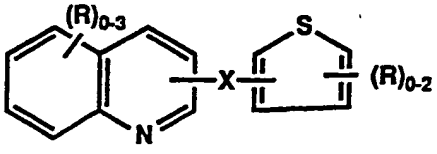
9. A method according to claim 6 where said compound is of the formula



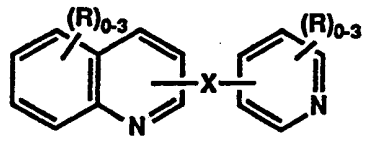
10. A method according to claim 6 where said compound is of the formula



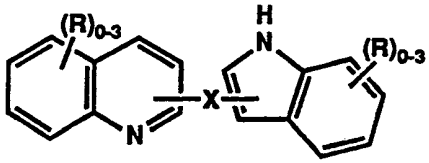
11. A method according to claim 7 where said compound is of the formula



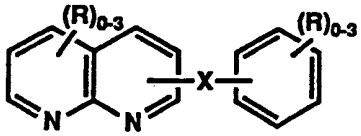
12. A method according to claim 6 where said compound is of the formula



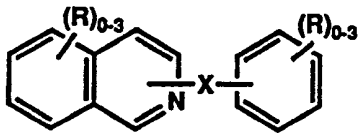
13. A method according to claim 6 where said compound is of the formula



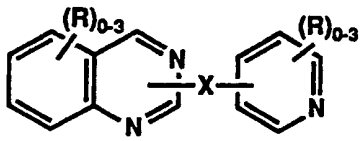
14. A method according to claim 6 where said compound is of the formula



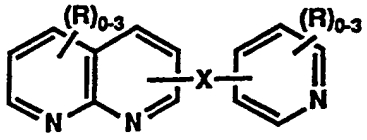
15. A method according to claim 6 where said compound is of the formula



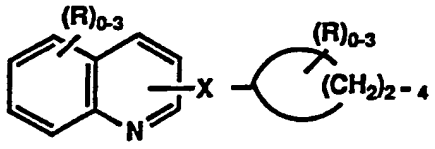
16. A method according to claim 6 where said compound is of the formula



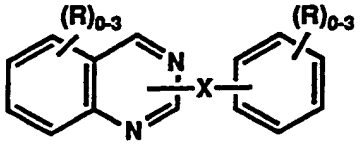
17. A method according to claim 6 where said compound is of the formula



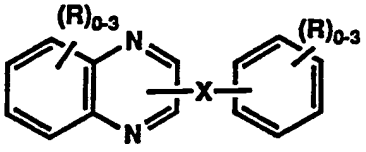
18. A method according to claim 6 where said compound is of the formula



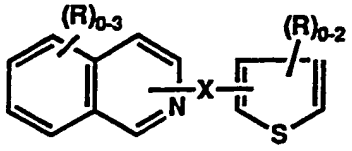
19. A method according to claim 6 where said compound is of the formula



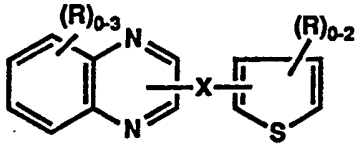
20. A method according to claim 6 where said compound is of the formula



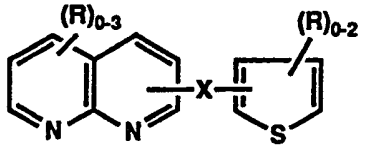
21. A method according to claim 6 where said compound is of the formula



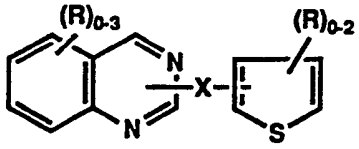
22. A method according to claim 6 where said compound is of the formula



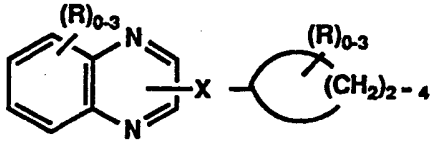
23. A method according to claim 6 where said compound is of the formula



24. A method according to claim 6 where said compound is of the formula



25. A method according to claim 6 where said compound is of the formula



26. A method according to claim 1 where said compound administered is selected from the group consisting of

3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-7-methoxyquinoline;
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(2-chlorothien-2-yl)-6,7-dimethoxyquinoline;
3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;

3-(2-chlorothien-2-yl)-5,7-dimethoxyquinoline;
2-phenyl-6,7-dimethylquinoxaline;
2-(thien-3-yl)quinoxaline;
6,7-dimethyl-2-(thien-3-yl)-quinoxaline;
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-7-methoxyquinoline;
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(2-chlorothien-2-yl)-6,7-dimethoxyquinoline;
3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
3-(2-chlorothien-2-yl)-5,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethylquinoline;
3-(1-cyclopent-1-enyl)-6,7-dimethoxyquinoline;
3-cyclopentyl-6,7-dimethoxyquinoline;
4-(3-phenylpropyloxy)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline-N-oxide;
3-(2-chlorothiophen-5-yl)-5,7-dimethoxyquinoline;
3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(3-fluorophenyl)-6,7-dimethoxyquinoline;
4-(2-phenylethoxy)-6,7-dimethoxyquinoline;
3-(4-methoxybenzyloxy)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
2-(thien-3-yl)-6,7-dimethoxyquinoxaline;
2-phenyl-6,7-dimethoxyquinoxaline;
6,7-dimethyl-2-(thien-3-yl)-quinoxaline;
2-phenyl-6,7-diethoxyquinoxaline;
2-(3-thienyl)-6,7-diethoxyquinoxaline;
2-(5-chloro-2-thienyl)-6,7-diethoxyquinoxaline;
2-(5-chloro-2-thienyl)-6,7-dimethoxyquinoxaline;
3-(3-fluoro-4-methoxyphenyl)-7-fluoroquinoline;
3-(thien-3-yl)-5,7-dimethylquinoline;
3-(5-chlorothien-2-yl)-6,7-dimethylquinoline;
3-(thien-3-yl)-6,7-difluoroquinoline or
3-(4-methoxyphyenyl)-7-methoxy-1-naphthalenol.

27. A method for the treatment of psoriasis in a patient suffering from such disorder comprising administering to said patient an effective anti-psoriatic composition according to claim 2.

28. A method for the treatment of atherosclerosis in a patient suffering from such disorder comprising administering to said patient an effective anti-atherosclerotic composition according to claim 2.

29. A method for the treatment of vascular reocclusion in a patient suffering from such disorder comprising administering to said patient an effective amount of a composition according to claim 2.

30. A method according to claim 29 where said disorder results from an angioplastic procedure.

31. A compound selected from the group consisting of:
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-7-methoxyquinoline;
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(2-chlorothien-2-yl)-6,7-dimethoxyquinoline;
3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
3-(2-chlorothien-2-yl)-5,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethylquinoline;
3-(1-cyclopent-1-enyl)-6,7-dimethoxyquinoline;
3-cyclopentyl-6,7-dimethoxyquinoline;
4-(3-phenylpropyloxy)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline-N-oxide;
3-(2-chlorothiophen-5-yl)-5,7-dimethoxyquinoline;
3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(3-fluorophenyl)-6,7-dimethoxyquinoline;
4-(2-phenylethoxy)-6,7-dimethoxyquinoline;
3-(4-methoxybenzyloxy)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
2-(thien-3-yl)-6,7-dimethoxyquinoxaline;
2-phenyl-6,7-dimethoxyquinoxaline;

6,7-dimethyl-2-(thien-3-yl)-quinoxaline;
2-phenyl-6,7-diethoxyquinoxaline;
2-(3-thienyl)-6,7-diethoxyquinoxaline;
2-(5-chloro-2-thienyl)-6,7-diethoxyquinoxaline;
2-(5-chloro-2-thienyl)-6,7-dimethoxyquinoxaline;
3-(3-fluoro-4-methoxyphenyl)-7-fluoroquinoline;
3-(thien-3-yl)-5,7-dimethylquinoline;
3-(5-chlorothien-2-yl)-6,7-dimethylquinoline;
3-(thien-3-yl)-6,7-difluoroquinoline or
3-(4-methoxyphyenyl)-7-methoxy-1-naphthalenol.

32. A pharmaceutical composition wherein the active ingredient is selected from the compounds of Claim 31.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/03736

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07C 43/21; C07D 215/18; 215/20; 43/21; A61K 31/44 31/50; 31/495
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Chemical Abstracts 1902-1991 Formula index.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,661,499 (YOUNG ET AL) 28 APRIL 1987 See entire reference.	31 & 32
A	N, CHEMCIAL Abstract, volume 103, Abst. No. 1232922, Barker et al., J. Chemical Soc. PERKIN. TRANS. 1985, (2), 275-81 (ENG.) See entire document.	31-32
A	M. CHEMICAL ABSTRACTS., Volume 108, N. Chemical Abstracts, No. 55860; Epling et al, J. HETEROLYCL. chem. 1987, 24(3) 853-7 (ENG.), See entire reference.	

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/03736

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

544/354; 353; 546/155; 167;180; 546/633; 514/248;249;300;307;311,314,345,347

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